

1. A histamine H₂ antagonist pharmaceutical dosage form providing a bi-modal pulsatile release profile comprising:

a. immediate release (IR) beads comprising an active-containing core particle; and

b. 5 timed pulsatile release (TPR) beads, wherein said TPR beads comprise:

i. an active-containing core particle; and

ii. a pulse coating surrounding said core,

wherein said IR beads provides a therapeutically effective amount of active to treat gastric acid secretions and the TPR beads provide a delayed dose of active 10 which provides a therapeutically effective amount of active to treat midnight GERD.

2. A pharmaceutical dosage form as defined in claim 1, wherein said histamine H₂ receptor antagonist is selected from the group consisting of nizatidine, cimetidine, ranitidine, and famotidine and derivatives thereof.

3. A pharmaceutical dosage form as defined in claim 1, wherein said timed pulsatile release (TPR) beads when tested in a USP Type II apparatus at 50 rpm using a 2-stage dissolution medium (first 2 hours and 700 ml 0.1 N HCl at 37°C followed by a dissolution in a pH of 6.8 obtained by the addition of 200 ml of pH modifier) exhibits a dissolution profile 5 substantially corresponding to the following pattern:

after 2 hours, 0-25% of the total active is released;
after 3 hours, 15-80% of the total active is released; and
after 4 hours, not less than 60% of the total active is released.

4. A pharmaceutical dosage form as defined in claim 3, wherein said dissolution profile substantially corresponds to the following pattern:

after 2 hours, 0-15% of the total active is released;
after 3 hours, 20-65% of the total active is released; and
5 after 4 hours, not less than 70% of the total active is released.

5. A pharmaceutical dosage form as defined in claim 4, wherein said dissolution profile substantially corresponds to the following pattern:

after 2 hours, 0-5% of the total active is released;
after 3 hours, 30-50% of the total active is released; and

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after 4 hours, not less than 80% of the total active is released.

6. A pharmaceutical dosage form as defined in claim 1, wherein said pulse coating comprises a water insoluble polymer and an enteric polymer.

7. A pharmaceutical dosage form as defined in claim 6, wherein said enteric polymer selected from the group consisting of esters of cellulose, polyvinyl acetate phthalate, pH-sensitive methacrylic acid-methylmethacrylate copolymers, shellac and derivatives thereof.

8. A pharmaceutical dosage form as defined in claim 7, wherein said enteric polymer is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose succinate and combinations thereof.

9. A pharmaceutical dosage form as defined in claim 1, wherein at least one of said polymers further comprises a plasticizer.

10. A pharmaceutical dosage form as defined in claim 9, wherein said plasticizer is selected from the group of triacetin, tributyl citrate, tri-ethyl citrate, acetyl tri-n-butyl citrate, diethyl phthalate, dibutyl sebacate, polyethylene glycol, polypropylene glycol, castor oil and acetylated mono- and di-glycerides and mixtures thereof.

11. A dosage form as defined in claim 6, wherein said water insoluble polymer and said enteric polymer are present in said pulse release coating at a ratio from 4:1 to 1:2.

12. A dosage form as defined in claim 11, wherein said ratio of water insoluble polymer to enteric polymer is from 2:1 to 1:1.

13. A dosage form as defined in claim 11, wherein said water insoluble polymer is ethylcellulose and said enteric polymer is hydroxypropyl methylcellulose phthalate.

14. A dosage form as defined in claim 13, wherein said ratio is approximately 1:1.

15. A dosage form as defined in claim 1, wherein said IR beads provide a loading dose by releasing substantially all of the active contained in said IR beads within the first hour after administration of the dosage form.

16. A dosage form as defined in claim 1, wherein said IR beads and TPR beads are present in a ratio from about 3:1 to 1:3.

17. A dosage form as defined in claim 16, wherein said IR beads and TPR beads are present in a ratio from about 2:1 to 1:2.

18. A dosage form as defined in claim 1, wherein the total weight of the coatings on the TPR beads is 10 – 60 weight % based on the total weight of the coated particles.

19. A method for the preparation of the dosage form of claim 1, comprising the steps of:

- a. preparing an active-containing core to form IR beads;
- b. coating the IR bead with a mixture of plasticized water soluble polymer and an enteric polymer to form a TPR bead; and
- c. filling capsules with IR beads and TPR beads at a ratio from 3:1 to 1:3.

5 20. The method of claim 19, wherein said active-containing core is produced by coating a particle selected from the group consisting of non-pareil seeds, acidic buffer crystals and alkaline buffer crystals with a water soluble film-forming composition comprising nizatidine and a polymeric binder.

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